HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

FINAL SUBMISSION

For

Phenol, Heptyl Derivatives

Prepared by
The American Chemistry Council
Petroleum Additives Panel
Health, Environmental and Regulatory Task Group

December 2006

LIST OF MEMBER COMPANIES IN THE
HEALTH, ENVIRONMENTAL AND REGULATORY TASK GROUP

The Health, Environmental, and Regulatory Task Group (HERTG) of the American Chemistry Council Petroleum Additives Panel includes the following member companies:

Afton Chemical Corporation (formerly Ethyl Corporation)

Chevron Oronite, LLC

Infineum USA LP

SI Group (formerly Schenectady International, Inc)

The Lubrizol Corporation

EXECUTIVE SUMMARY

The American Chemistry Council Petroleum Additives Panel Health, Environmental and Regulatory Task Group (HERTG), and its member companies hereby submit this final submission for "*Phenol, heptyl derivatives"* (applicable CAS#s include 72624-02-3 and 1987-50-4) under the United States Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program.

Manufacture and Use Profile: *Phenol, heptyl derivatives* (HPL) is made through the acid-catalyzed alkylation of phenol with industrial grade heptenes. The principal use of HPL is as a building block to manufacture higher molecular weight oligomeric lubricating additive components. The additives derived from HPL are used as detergents and metal deactivators in a wide variety of lubricating applications including industrial and automotive gear oils, automatic transmission formulations, and small engine applications.

Fate and Transport Characteristics: HPL has the potential for inherent biodegradation based upon studies using bacterial sludge and in seawater. HPL does not have hydrolysable functional groups and hydrolysis is not likely to be a significant fate process if released into the aquatic environment. The Atmospheric Oxidation Potential of this substance was estimate by EPIWIN to be rapidly degraded in the atmosphere. The relative distribution of HPL among environmental compartments, estimated using the Level I Equilibrium Criterion model, predicts the equilibrium distribution of a fixed quantity of a chemical in a closed environment at equilibrium, with no degrading reaction, advective processes and no intermedia transport.

Aquatic toxicity: Acute testing on HPL indices that this substance is toxic to freshwater fish, fresh water invertebrates and freshwater algae under the conditions of the assays.

Mammalian toxicity - Acute: Data on mammalian toxicity indicates that HPL is of low concern for acute toxicity.

Genotoxicity: HPL was not mutagenic in an Ames bacterial assay with or without metabolic activation. In a human lymphocyte chromosomal aberration assay HPL did not induce a statistically significant increase in the frequency of lymphocytes with chromosomal aberrations, either in the presence or absence of liver metabolizing enzymes.

Mammalian toxicity – Repeated dose systemic and reproduction/developmental endpoints: Following 28-days of daily oral gavage administration, HPL elicited toxicity primarily at 450 mg/kg/day (highest dose tested) as evidenced by lethality, clinical observations (decreased defecation, dermal atonia, hypothermia), lower body weights, serum chemistry changes (urea nitrogen, creatinine and elevations of serum hepatic enzymes) and several histological changes (tubular nephropathy in the kidneys, fatty change of the liver, stratified squamous hyperplasia of the non-glandular stomach, thymic lymphoid depletion, and hemorrhage and depletion of seminal vesicle secretion). The No Observed Adverse Effect Level was assigned at 150 mg/kg/day.

No reproduction or developmental toxicity studies have been performed on HPL. However, data for these endpoints is available for a highly homologous alkylphenol, namely octylphenol (OP). The chemical structures of HPL and OP vary only by a single carbon atom on the alkyl side chain. The physical chemical properties of HPL and OP are also similar. Based upon the similarity of structure and physicochemical properties, there is a basis for using reproduction and developmental toxicity data on OP as read-across to the highly homologous compound HPL. A 2-generation reproduction toxicity feeding study in rats has been conducted on OP and the details of the study are in the public domain. Parental systemic toxicity was manifested by reductions in body weight, body weight gains and feed consumption at the highest dose. There were no effects of treatment in F0 or F1 females on mating, fertility, pregnancy or gestational indices. There were no effects of treatment in F0 or F1 males on mating or fertility indices. There were no treatment-related effects on organ weights, macroscopic, or microscopic findings of reproductive organs. There were no effects on sperm production or functional indices in any generation. For F1 and F2 offspring, there were no effects of treatment on live birth indices or sex ration. However, pup body weights per litter were significantly reduced at 2000 ppm (~150 mg/kg/day) for F1 and F2 litters. Reduced pup weights were also observed during the latter portion of the lactational period at the highest dose. Acquisition of vaginal patency and preputial separation was significantly delayed at 2000 ppm dose. The No Observed Adverse Effect Level (NOAEL) for systemic and postnatal toxicity was 200 ppm (~15 mg/kg/day). The NOAEL for reproductive toxicity was 2000 ppm (~150 mg/kg/day). Based upon the structural and physicochemical properties HPL shares with OP, it is reasonable to conclude that the reproduction and developmental toxicity of these two chemicals will be similar.

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1.0 INTRODUCTION

In March 1999, the American Chemistry Council (formerly the Chemical Manufacturers Association) Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its participating member companies committed to address data needs for certain chemicals listed under the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program.

This final submission describes how the HERTG addressed physicochemical, environmental fate, environmental effects and mammalian toxicity testing information for *"Phenol, heptyl derivatives"*.

In preparing the final submission the following steps were undertaken:

Step 1: A review of the literature and confidential company data was conducted on the physicochemical properties, mammalian toxicity endpoints, and environmental fate and effects for *"Phenol, heptyl derivatives"*, using its CAS numbers, CAS names, and synonyms. Searches included the following sources: MEDLINE, BIOSIS, CANCERLIT, CAPLUS, CHEMLIST, EMBASE, HSDB, RTECS, EMIC, TOXLINE, TSCATS databases as well as standard handbooks and databases (e.g., Sax, CRC Handbook on Chemicals, IUCLID, Merck Index).

Step 2: The compiled data was evaluated for adequacy in accordance with the EPA guidance documentation.

2.0 GENERAL SUBSTANCE INFORMATION

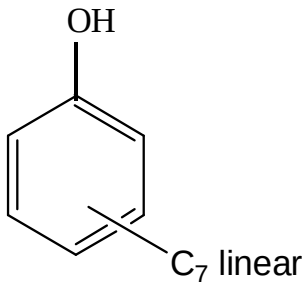
The substance that is the subject of this test plan is used as a precursor molecule in the manufacture of petroleum additives used in highly refined lubricating base oil. The chemical name, CAS Registry Number, molecular weight and chemical structure for this substance are presented below.

Chemical Name: Phenol, heptyl derivatives (HPL)

Chemical Abstract Service Registry Number: 72624-02-3
Alternative Chemical Abstract Service Registry Number: 1987-50-4

Molecular Weight**:** 192.3 gm/mol

Chemical Structure:

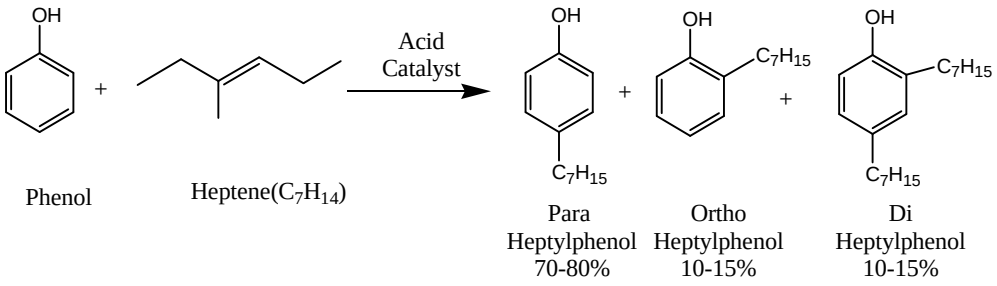


72624-02-3

3.0 USE and EXPOSURE INFORMATION

Manufacture: Phenol, heptyl derivatives (HPL) is made through the acid-catalyzed alkylation of phenol with industrial grade heptenes. The heptenes used to make HPL are a complex mixture of branched isomers obtained from the acid catalyzed polymerization of propylene–butylene mixtures. The general reaction process is shown in Figure 1, together with the typical levels of the major components.

Figure 1



Based on supplier information, HPL has a relatively narrow homolog distribution, where C7 alkylphenol comprises greater than 95% of the total olefins in the mixture. No significant contaminates or by-products are present, and combined levels of unreacted heptene and phenol are generally less than 1% of the total mixture.

Use in Lubricants: The principal use of HPL is as a building block to manufacture higher molecular weight oligomeric lubricating additive components. These components are highly stable and not expected to release HPL under normal use in these applications. The level of unreacted HPL in these products is less than 1%.

HPL is used to manufacture a variety of lubricant additives. These additives are typically blended with other additives into lubricant concentrates, which are then sold to lubricant marketers who then blend them with oil and, in some cases, additional additives, to yield the final (finished) lubricant. This finished lubricant is then sold to the end user for use in the lubricant application.

The additives derived from HPL are used as detergents and metal deactivators in a wide variety of lubricating applications including industrial and automotive gear oils, automatic transmission formulations, and small engine applications. The average level of unreacted HPL in these finished lubricants is estimated to be very low.

4.0 PHYSICOCHEMICAL PROPERTIES

4.1 Summary of Available Data[1]

4.1.1 Melting Point

HPL is a liquid at ambient temperature. The freezing point of HPL is < -5°C.

4.1.2 Boiling Point

The boiling point range of HPL is 256 – 280°C.

4.1.3 Vapor Pressure

The vapor pressure of HPL is 0.0113 mmHg @ 25°C.

4.1.4 Water Solubility

The water solubility of HPL is 12.2 mg/L as measured by the shake flask method.

4.1.5 Octanol/Water Partition Coefficient

The log octanol/water partition coefficient of HPL has been estimated at 4.5 (Tollefsen et al[2].)

5.0 ENVIRONMENTAL FATE DATA

5.1 Biodegradability

An adequate and reliable biodegradation test has been conducted on HPL according to OECD Test Guideline 301B and ASTM D5864 guidelines using adapted inoculum. The results indicate that this material is inherently biodegradable based on a degradation of 25% after 28 days. In addition to above, studies available in the literature[3] indicate approximately 40% biodegradation in seawater over 28-days. Additional biodegradation testing is not proposed.

[1] Schenectady International Inc. (2003) Technical Data Sheet: Para-heptylphenol (CAS# 72624-02-3).
[2] Tollefsen et al. Acute Toxicity and Toxicokinetics of 4-Heptyl phenol in Juvenile Atlantic Cod (Gadus Morhua L.). Environmental Toxicology and Chemistry Vol 17, No. 4. pp. 740-746. 1998.
[3] Brendshag, et al. Toxicity Testing and chemical characterization of produced water – A preliminary study In Ray JP, Engelhart FR Eds. Produced Water. Technological/Environmental Issues and Solutions. Plenum. New York, NY, USA. Pp 245-260.

5.2 Hydrolysis

Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters[4] Chemically, this substance does not have hydrolysable functional groups and hydrolysis is not likely to be a significant fate process if released into the aquatic environment.

5.3 Photodegradation

The Atmospheric Oxidation Potential (AOP) of this substance was characterized using EPA's Quantitative Structure Activity Relationship (QSAR) program, EPIWIN[5]. Atmospheric photooxidation is the degradation of a chemical in air due to reaction with ozone or hydroxyl radicals and is dependent on the chemical structure, concentration and hydroxyl radical concentration. An overall hydroxyl rate constant of 48.8 x 10^{-12} cm^3/molecule-sec was calculated with a half-life of 2.6 hours. This indicates that atmospheric HPL will be rapidly degraded and will not be persistent.

5.4 Fugacity Modeling

The relative distribution of HPL among environmental compartments was evaluated using Level I Equilibrium Criterion (EQC) model[6]. Fugacity modeling was conducted using experimentally derived physico-chemical input parameters for vapor pressure, water solubility and octanol-water partition coefficient. The level I model predicts the equilibrium distribution of a fixed quantity of a chemical in a closed environment at equilibrium, with no degrading reaction, advective processes and no intermedia transport. The medium receiving the emission is unimportant because the chemical is assumed to be instantaneously distributed to an equilibrium condition. A Level III fugacity modeling is not appropriate as potential discharge rates into various environmental compartments and the reaction half-life estimates are not known for this chemical.

The Level I modeling results are presented below which indicate the likely environmental compartment into which a chemical will tend to partition and an indication of the distribution in each medium.

Chemical	Air (%)	Water (%)	Soil (%)	Sediment (%)	Sesp. Sediment (%)	Fish (%)
HPL	13.9	2.9	81.4	1.8	0.06	0.0046

[4] Neely, W. B. 1985. Hydrolysis. In: W. B. Neely and G. E. Blau, Eds. Environmental Exposure from Chemicals. Vol I., pp. 157-173. CRC Press, Boca Raton, FL, USA.
[5] Estimation Program Interface for Windows (EPIWIN), Version 3.02. Syracuse Research Corporation, Syracuse, NY.
[6] Mackay, D.A et al. Assessing the Fate of New and Existing Chemicals: A Five-Stage Process. Environ. Toxicol. Chem. 15, 1618-1626 (1996).

6.0 AQUATIC TOXICITY DATA

6.1 Acute Fish Toxicity

A 96-hour median lethal concentration of 0.56 mg/L was obtained in a flow through acute toxicity study conducted with juvenile fish, Atlantic cod (*Gadus morhua L.*). CITE REFERENCE

6.2 Acute Invertebrate Toxicity

HPL was tested for effects on aquatic invertebrates (*Daphnia magna*) following OECD Test Guideline 202.The 24 and 48-hour EC_{50} was determined to be 0.64 and 0.38 mg/L, respectively. The No Observed Effect Concentration (NOEC) (nominal loading rate) after 24 and 48 hours were, accordingly 0.30 and 0.17 mg/L.

6.3 Algal Toxicity

HPL was tested for effects on aquatic algae (*Scenedesmus subspicatus*) following OECD Test Guideline 201. Based on nominal concentrations in water, HPL reduced biomass by 50% (E_bC_{50} 72 hours) at a concentration of 0.25 mg/L. The concentration that reduced specific growth by 50% (E_rC_{50} 72 hours) was 1.2 mg/L. The No Observed Effect Concentration (NOEC) was 0.048 mg/L.

7.0 MAMMALIAN TOXICOLOGY DATA

7.1 Acute Mammalian Toxicity

Acute oral and dermal toxicity studies are available for HPL. In these studies, the LD_{50}s are between 0.2g/kg and 2.0g/kg, respectively.

7.2. Genotoxicity

An adequate and reliable Ames mutagenicity assay was performed for HPL. The test substance was not mutagenic in the assay with or without metabolic activation.

A human lymphocyte chromosomal aberration assay was also performed using HPL using OECD Test Method Guidance 473. HPL did not induce a statistically significant increase in the frequency of lymphocytes with chromosomal aberrations, either in the presence or absence of liver metabolizing enzymes.

7.3 Repeated-dose and Reproductive/Developmental Toxicity

7.3.1 Systemic toxicity

HPL was evaluated for repeated-dose systemic toxicity using an experimental design consistent with OECD Test Method Guideline 407. Following 28-days of daily oral gavage administration, HPL elicited toxicity primarily at the 450 mg/kg/day dosage level as evidenced by lethality, clinical observations (decreased defecation, dermal atonia, hypothermia), lower body weights, serum chemistry changes (urea nitrogen, creatinine and elevations of serum hepatic enzymes) and several histological changes (tubular nephropathy in the kidneys, fatty change of the liver, stratified squamous hyperplasia of the non-glandular stomach, thymic lymphoid depletion, and hemorrhage and depletion of seminal vesicle secretion). The No Observed Adverse Effect Level was assigned at 150 mg/kg/day.

7.3.2. Reproduction/Developmental Toxicity

No reproduction or developmental toxicity studies have been performed on HPL. However, data for these endpoints is available for a highly homologous alkylphenol, namely octylphenol (OP). The chemical structures of HPL and OP vary only by a single carbon atom on the alkyl side chain. The physical chemical properties of HPL and OP are also similar.

Chemical Name	CASRN	Starting Olefin	MW	Boiling Point	Log Ko/w	Water Solubility
HPL	72624-02-3	heptylene	192	256-280^{o}C	4.5	12.2 mg/L
OP[7]	140-66-9	isobutylene	206	282^{o}C	4.12	18 mg/L

Based upon the similarity of structure and physicochemical properties, there is a basis for using reproduction and developmental toxicity data on OP as read-across to the highly homologous compound HPL.

A 2-generation reproduction toxicity study in rats has been conducted on OP[8]. Male and female rats Sprague-Dawley rats were administered OP in the feed at 0, 0.2, 20, 200 and 2000 ppm (approximating 0, 0.15, 1.5, 15 and 150 mg/kg/day) for two generations (F0 parental animals through F2 adulthood.). Adult systemic toxicity was manifested by reductions in body weight, body weight gains and feed consumption at the highest dose. There were no effects of treatment in F0 or F1 females on mating,

[7] Brooke D, Watts C, Mitchell R, Johnson I (2003) Environmental Risk Assessment Report: 4-tert-octylphenol (CASRN 140-66-9). National Centre for Ecotoxicology and Hazardous Substances. United Kingdom Environment Agency.

[8] Tyl RW, Myers CB, Marr MC, Brine DR, Fail PA, Seely JC, Van Miller JP (1999) Two-generation reproduction study with para-tert-octylphenol in rats. Regul. Toxicol. Pharmacol. 30 (2 Pt 1) 81-95.

fertility, pregnancy or gestational indices. There were no effects of treatment in F0 or F1 males on mating or fertility indices. There were no treatment-related effects on organ weights, macroscopic, or microscopic findings of reproductive organs. There were no effects on sperm production or functional indices in any generation. For F1 and F2 offspring, there were no effects of treatment on live birth indices or sex ration. However, pup body weights per litter were significantly reduced at 2000 ppm for F1 and F2 litters. Reduced pup weights were also observed during the latter portion of the lactational period at the highest dose. Acquisition of vaginal patency and preputial separation was significantly delayed at 2000 ppm dose. The No Observed Adverse Effect Level (NOAEL) for systemic and postnatal toxicity was 200 ppm (~15 mg/kg/day). The NOAEL for reproductive toxicity was 2000 ppm (~150 mg/kg/day). Based upon the structural and physicochemical properties HPL shares with OP, it is reasonable to conclude that the reproduction and developmental toxicity of these two chemicals will be similar.

8.0 CONCLUSION

Adequate information is available for the physicochemical properties of melting point, boiling point, vapor pressure, water solubility and octanol/water partition coefficient for HPL. The structural and experimental physicochemical properties of HPL were used to model hydrolytic, photodegradation and fugacity potential. HPL is not readily biodegradable, but experimental evidence suggests the potential for inherent biodegradability. HPL is toxic to fish, invertebrates and algae. Oral and dermal studies indicate that HPL is of low concern for acute toxicity. HPL is neither mutagenic or clastogenic. Systemic toxicity resulting from repeated dosing of HPL is limited to high doses (e.g., 450 mg/kg/day) and characterized by mild clinical observations and changes in serum chemistry endpoints and test material related changes in the histological appearance of the liver, kidney, stomach, thymus and seminal vesicles. Reproduction and developmental toxicity studies were not performed on HPL, rather a read-across argument supports the use of existing robust 2-generation toxicity data from a highly homologous chemical OP. The analogue chemical had minimal effect .